ORIGINAL

Efficacy of ezetimibe as monotherapy or combination therapy in hypercholesterolemic patients with and without diabetes

Miyako Kishimoto, Takehiro Sugiyama, Keiichiro Osame, Daisuke Takarabe, Masahide Okamoto, and Mitsuhiko Noda

Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo, Japan

Abstract : Ezetimibe selectively inhibits dietary and biliary cholesterol absorption and reduces serum cholesterol levels when administered alone (monotherapy) and along with common lipid-regulating agents (combination therapy). To evaluate the effect of ezetimibe therapy on the lipid profile, glucose metabolism, and levels of cholesterol absorption and synthesis markers, we administered 10 mg ezetimibe to 50 hypercholesterolemic patients with or without diabetes. The serum levels of low-density lipoprotein cholesterol and total cholesterol were significantly reduced at 4 and 12 weeks of ezetimibe therapy in diabetic patients of both the monotherapy and combination-therapy groups and in nondiabetic patients of the combination-therapy group. The serum levels of the cholesterol absorption markers were significantly reduced, while those of the cholesterol synthesis markers were significantly increased at 12 weeks of ezetimibe therapy. No significant differences were noted in the values of the parameters of glucose metabolism in all patients. We also investigated the clinical characteristics of patients who exhibited a good response to ezetimibe (ezetimibe responders) ; however, multivariate regression analysis did not reveal a correlation between ezetimibe efficacy and patient characteristics such as gender, age, BMI, diabetic condition, method of ezetimibe administration, and the initial absolute values of cholesterol absorption/synthesis markers levels. In conclusion, ezetimibe therapy significantly improved the lipid profile without disturbing glucose metabolism. We were unable to identify the specific characteristics of ezetimibe responders among our subjects. However, we may interpret this result as suggesting that ezetimibe can be used in any population to lower low-density lipoprotein cholesterol levels. J. Med. Invest. 58 : 86-94, February, 2011

Keywords **:** *ezetimibe, hypercholesterolemia, cholesterol absorption, cholesterol synthesis*

INTRODUCTION

Patients with type 2 diabetes mellitus are at increased risk for cardiovascular disease (1, 2), which is attributed in part to lipid abnormalities commonly associated with type 2 diabetes and metabolic syndrome (3). Reduction in the low-density lipoprotein

Received for publication October 26, 2010 ; accepted December 14, 2010.

Address correspondence and reprint requests to Miyako Kishimoto, Chief, Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan and Fax : +81-3-3207-1038.

cholesterol (LDL-c) levels constitutes the basis for the prevention of cardiovascular disease (4). Aggressive therapy to lower the LDL-c levels was associated with a subsequent reduction in the rates of cardiovascular events in recent comparative trials of different statins or the same statin at different doses (5-8). However, when the statin dose is increased to the maximum approved level, there is only limited additional lowering of LDL-c with an increase in the incidence of side effects (9).

The recently introduced ezetimibe (10, 11), which selectively inhibits dietary and biliary cholesterol absorption by binding to the Niemann-Pick C1-like 1 (NPC1L1) protein (12-15) at the brush-border membrane of enterocytes, appears to be an interesting add-on therapy to low-dose statins to obtain significant improvement in the different lipid parameters without increasing the statin dose, and thus, to prevent dose-related side effects (16, 17). In this study, we evaluated the changes in the lipid profile, glucose metabolism, and marker levels that reflect on the effect of ezetimibe treatment on the absorption and synthesis of cholesterol in hypercholesterolemic patients with or without diabetes. We also investigated the clinical characteristics of patients who show a better response to ezetimibe (ezetimibe responders) and who thus are more likely to benefit from the treatment than other patients.

METHODS

The outpatients of National Center for Global Health and Medicine with LDL-c levels higher than the levels recommended in the Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular disease (18) were the subjects of this study. The patients in the monotherapy group were administered only ezetimibe (10 mg/day). The patients in the combination therapy group were administered ezetimibe as an add-on therapy to common lipid-regulating agents including low-dose statins (simvastatin, pravastatin, atorvastatin, pitavastatin, and rosuvastatin) and fenofibrates.

The patients were allowed to continue with their other medications and daily activities during the study. A physical examination of all the patients including measurements of height, body weight, body mass index (BMI) (calculated as the ratio of weight to the square of height), and blood pressure was conducted at the start and at 4 weeks and 12 weeks after ezetimibe administration ; in addition, blood tests were performed for liver and kidney function, serum lipids, fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c) (19) by routine laboratory methods. C-reactive protein (CRP), remnant-like lipoprotein cholesterol (RLP-c), insulin, glycated albumin (GA), markers for cholesterol absorption (cholestanol, campesterol, and sitosterol), and 1 marker for cholesterol synthesis (lathosterol) were also assessed. RLP-c was analyzed by the immunoabsorption method using Hitachi automatic analyzer 7170 (Hitachi Ltd., Tokyo), and cholesterol synthesis and absorption markers were analyzed in a GC-2010 capillary gas chromatograph (Shimadzu Co., Kyoto) by gas-liquid chromatography. Blood was sampled in fasting conditions for all measurements. Ezetimibe safety and tolerance were evaluated throughout the study by analysis of the patient reports and results of measurements of liver and kidney function.

Statistical analysis was performed with Student's paired *t*-test or the Wilcoxon signed rank test using STATA version 11 (StataCorp LP, College Station, TX). LDL-c levels were calculated by the Friedewald equation, and triglyceride values were logarithmically transformed to obtain a normal distribution before statistical analysis. The rates of changes in LDL-c and those of each lipid were calculated by dividing the difference between the latter and former value by the former value. A p value of <0.05 were considered statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki, and the patients provided their written informed consent after the purpose and potential risks of the study were explained to them.

RESULTS

Table 1 lists the basic characteristics of the patients of the monotherapy and combination therapy groups. In the monotherapy group, 20 of 24 patients and in the combination therapy group, 15 of 26 patients were diabetic. These diabetic patients were treated with diet and exercise, and some were treated with antidiabetic agents. Table 2 shows changes in BMI, BP, liver and kidney function, and CRP levels. The BMI and blood pressure of the patients did not change significantly during the study. During the ezetimibe administration, no serious adverse events related to liver and kidney dysfunction were noted in any patient. There were no significant

Table 1 Patient characteristics at baseline
The values represent mean± SD ; these values were obtained at the baseline, i.e., before ezetimibe monotherapy and before combination therapy. DM, diabetes mellitus ; SBP, systolic blood pressure ; DBP, diastolic blood pressure

Monotherapy

	All (N=24)	DM (N=20)	non-DM (N=4)
Age (yrs)	59.7± 11.0	61.4± 9.5	51.0± 15.7
Male/Female	10/14	10/10	0/4
Bodyweight (kg)	66.8± 14.8	68.0± 15.1	60.7± 13.3
BMI (kg/m^2)	25.8± 4.9	25.7± 4.8	26.3± 6.1
SBP (mmHg)	124.4± 17.0	126.9± 17.0	112.0± 12.1
DBP (mmHg)	71.6± 9.3	72.1± 10.1	69.0± 2.0

Combination therapy

	All (N=26)	DM (N=15)	non-DM (N=11)
Age (yrs)	62.4± 11.6	66.7± 11.3	63.0± 14.3
Male/Female	10/16	6/9	4/7
Bodyweight (kg)	62.5± 11.6	61.7± 8.3	63.6± 15.8
BMI (kg/m^2)	24.9± 3.7	25.0± 4.8	24.8± 4.5
SBP (mmHg)	127.1± 11.9	124.9± 12.2	130.4± 11.3
DBP (mmHg)	70.9± 9.3	68.9± 10.6	73.8± 6.4

Table 2 Changes in the measurements of the physical and laboratory test parameters for all patients
The values represent mean± SE.

	at baseline	4 weeks	12 weeks
BMI (kg/m^2)	25.35± 0.61	25.37± 0.61	25.37± 0.63
SBP (mmHg)	125.8± 2.1	123.9± 2.0	126.9± 2.2
DBP (mmHg)	71.2± 1.3	67.0± 1.4	70.4± 1.3
AST (U/L)	23.8± 1.5	24.5± 1.5	23.8± 8.9
ALT (U/L)	23.6± 2.2	25.6± 2.4	24.8± 1.9
γ-GTP (U/L)	44.6± 7.6	41.3± 6.7	46.9± 7.9
LDH (U/L)	206.3± 7.3	208.7± 7.3	217.5± 8.7
ALP (U/L)	216.4± 10.3	221.1± 10.4	222.4± 10.8
ChE (U/L)	350.8± 7.9	343.3± 9.6	355.1± 8.0
CPK (U/L)	108.6± 7.3	111.6± 7.5	111.1± 8.7
BUN (mg/dl)	14.0± 0.7	14.3± 0.7	14.5± 0.6
Cr (mg/dl)	0.72± 0.03	0.73± 0.04	0.73± 0.04
UA (mg/dl)	4.90± 0.15	4.87± 0.17	4.90± 0.16
CRP (mg/dl)	0.17± 0.05		0.12± 0.02

changes in the CRP levels at 12 weeks of ezetimibe administration in all patients.

Lipid profile

In all patients (Table 3), LDL-c levels were significantly reduced from 155.2±3.7(mean±S.E.) mg/dL at baseline to 120.5± 3.9 mg/dL at 4 weeks of treatment and to 123.5± 3.6 mg/dL at 12 weeks of treatment. In all patients, total cholesterol (TC) levels were also reduced significantly from 241.6± 4.6 mg/dL at baseline to 205.5± 4.4 mg/dL at 4 weeks of treatment and to 210.8± 4.6 mg/dL at 12 weeks of treatment. A significant reduction of LDL-c and TC levels was noted at 4 and 12 weeks of treatment in diabetic patients in both the monotherapy and combination therapy groups and non-diabetic patients in only the combination therapy group (Table 4). No significant changes were noted in the levels of high-density lipoprotein cholesterol (HDL-c) levels and RLP-c levels overall, but a significant reduction at 12 weeks of treatment as compared to the initial levels was noted in HDL-c and RLP-c levels in the diabetic patients of the monotherapy. No significant changes were observed in the triglyceride levels in all patients throughout the study period.

Glucose metabolism

At 12 weeks of ezetimibe administration in all patients, no significant changes were noted in the FPG, HbA1c, GA, level of insulin resiatance and β-cell function as estimated using the homeostatic model assessment (HOMA) (20) of insulin resistance (IR) and HOMA of β-cell function (β) (Table 5).

Table 3 Changes in the lipid profile and in the levels of markers of cholesterol absorption/synthesis in all patients
The values represent mean± SE ; these values were obtained at the baseline and at 4 and 12 weeks. The values under "Change (%) at 4 w" and "Change (%) at 12 w" are presented as percent changes from the baseline to 4 weeks and from the baseline to 12 weeks (mean± SD), respectively. Endpoint measurement for every variable was not obtained in the case of all patients. Statistical analysis was performed using the paired *t*-test (*p< 0.05).

	at baseline	4 weeks	change (%) at 4 w	12 weeks	Change (%) at 12 w
TC (mg/dl)	241.6± 4.6	205.5± 4.4*	-14.4± 10.8	210.8± 4.6*	-12.5± 11.5
LDL-c (mg/dl)	155.2± 3.7	120.5± 3.9*	-21.7± 15.3	123.5± 3.6*	-19.4± 15.7
HDL-c (mg/dl)	57.0± 1.7	57.0± 1.8	0.6± 11.3	55.7± 1.9	-1.9± 11.7
Triglyceride (mg/dl)	146.9± 8.2	140.0± 9.1	-3.3± 28.1	153.7± 10.6	6.6± 40.1
RLP-c (mg/dl)	6.51± 0.43			5.94± 0.52	-5.4± 43.7
Cholestanol (μg/ml)	3.14± 0.12			2.82± 0.11*	-6.6± 26.6
Sitosterol (μg/ml)	3.64± 0.30			2.04± 0.13*	-38.5± 19.7
Campesterol (μg/ml)	5.58± 0.56			2.63± 0.19*	-45.6± 20.9
Lathosterol (μg/ml)	3.00± 0.28			3.95± 0.33*	51.1± 79.3

Table 4 Changes in the lipid profile and in the levels of cholesterol absorption/synthesis markers of the monotherapy group and combination group
The values represent mean± SE ; these values were obtained at the baseline and at 4 and 12 weeks. Endpoint measurement for every variable was not obtained in the case of all patients. Statistical analysis was performed using the paired *t*-test (*p< 0.05).

Monotherapy

	DM			non-DM		
	Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
TC (mg/dl)	236.3± 6.8	199.9± 6.3*	201.6± 6.0*	250.3± 16.5	224.3± 17.8	225.8± 14.4
LDL-c (mg/dl)	152.9± 5.1	119.3± 4.9*	123.1± 4.7*	157.7± 21.1	133.5± 16.9	134.2± 17.6
HDL-c (mg/dl)	57.7± 2.4	55.3± 2.3	54.9± 2.7*	61.0± 7.0	61.8± 9.0	62.2± 8.2
Triglyceride (mg/dl)	133.5± 12.9	122.9± 15.1	122.5± 9.8	157.8± 33.1	145.3± 26.4	146.5± 25.2
RLP-c (mg/dl)	6.38± 0.76		4.98± 0.46*	6.30± 1.01		5.78± 1.20
Cholestanol (μg/ml)	3.06± 0.19		2.73± 0.18	2.48± 0.20		2.85± 0.39
Sitosterol (μg/ml)	3.86± 0.39		2.01± 0.14*	2.25± 0.38		1.63± 0.34*
Campesterol (μg/ml)	5.83± 0.74		2.56± 0.23*	3.60± 0.60		2.23± 0.17*
Lathosterol (μg/ml)	3.26± 0.38		4.41± 0.51*	3.23± 0.54		4.28± 0.45*

Combination therapy

	DM			non-DM		
	Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
TC (mg/dl)	227.9± 7.1	191.7± 6.1*	208.9± 8.2*	266.6± 9.8	227.9± 10.2*	225.2± 12.8*
LDL-c (mg/dl)	144.3± 4.9	108.2± 6.3	117.3± 6.9	171.9± 7.9	133.8± 10.3	127.7± 9.2
HDL-c (mg/dl)	51.7± 2.6	54.1± 2.6	52.9± 2.7	61.3± 4.7	61.9± 4.9	60.6± 5.2
Triglyceride (mg/dl)	146.1± 14.0	145.2± 16.9	176.4± 26.4	167.2± 18.3	161.2± 18.2	184.3± 21.4
RLP-c (mg/dl)	6.15± 0.85		6.57± 1.49	7.31± 0.72		6.90± 0.92*
Cholestanol (μg/ml)	3.30± 0.28		3.08± 0.22	3.32± 0.17		2.62± 0.20*
Sitosterol (μg/ml)	4.13± 0.84		2.38± 0.33*	3.18± 0.35		1.83± 0.26*
Campesterol (μg/ml)	6.46± 1.52		3.08± 0.50*	4.76± 0.73		2.34± 0.33*
Lathosterol (μg/ml)	2.65± 0.69		3.87± 0.82*	2.89± 0.52		3.12± 0.50

Table 5 Levels of glucose metabolism in patients of the monotherapy group and combination group
The values represent median (interquartile range). Statistical analysis was performed using the Wilcoxon-signed rank test. The value for HbA1c (%) is estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP).

Monotherapy

	DM			non-DM		
	Baseline	After 12 weeks	*p* value	Baseline	After 12 weeks	*p* value
FPG (mg/dL)	136.5 (122.5-153.0)	138.0 (123.0-151.0)	0.6435	96.0 (89.9-100.0)	95.5 (91.0-98.0)	0.8527
HbA1c (%)	6.7 (6.7-7.35)	7.1 (6.6-7.5)	0.6002	5.65 (5.45-5.95)	5.65 (5.50-5.85)	0.8539
GA (%)	19.4 (17.6-20.5)	18.9 (17.6-19.5)	0.2431	14.9 (12.2-17.6)	14.4 (14.3-16.8)	0.4652
HOMA-IR	1.99 (1.34-2.78)	2.09 (1.52-4.11)	0.5732	1.71 (1.02-2.76)	1.75 (1.13-3.62)	0.4652
HOMA-β	33.1 (19.1-42.3)	32.0 (25.1-50.4)	0.6874	65.8 (46.1-176.9)	77.52 (53.6-212.0)	0.1441

Combination therapy

	DM			non-DM		
	Baseline	After 12 weeks	*p* value	Baseline	After 12 weeks	*p* value
FPG (mg/dL)	132.0 (115.0-156.0)	136.0 (108.0-176.0)	0.8505	98.0 (92.0-101.0)	100.5 (90.0-107.0)	0.2371
HbA1c (%)	7.3 (6.7-7.6)	7.5 (6.7-7.9)	0.1631	5.8 (5.6-6.1)	5.9 (5.7-6.1)	0.1301
GA (%)	18.3 (17.2-22.4)	20.3 (16.3-24.0)	0.2557	13.9 (12.9-15.6)	14.0 (12.7-14.8)	0.2017
HOMA-IR	1.98 (1.32-2.64)	2.45 (1.05-2.96)	0.124	1.60 (0.87-2.59)	2.49 (1.40-3.67)	0.1394
HOMA-β	30.0 (18.7-42.8)	28.7 (15.0-58.0)	0.3305	70.0 (33.1-135.6)	93.2 (61.9-129.1)	0.2411

Changes in the cholesterol absorption and synthesis marker levels

A significant reduction of 6.6± 26.6 (mean± S.D.) % in the levels of cholestanol, a marker for cholesterol absorption, was noted at 12 weeks of ezetimibe administration in all patients (Table 3) ; in addition, a significant reduction was also noted in the non diabetic patients in the combination therapy group (Table 4). A significant reduction of 38.5± 19.7% and 45.6± 20.9% was noted in the levels of other cholesterol markers, sitosterol and campesterol, respectively in all patients (Table 3). A significant elevation of 51.1± 79.3% as compared to the initial levels was noted in the levels of lathosterol, a marker for cholesterol synthesis, at 12 weeks of treatment in all patients except the nondiabetic patients of the combination therapy group (Table 4). Scattergram illustrating a relation between the rates of changes in the levels of LDL cholesterol and cholesterol absorption/synthesis markers (Fig. 1). There was a positive relation between the rates of changes in the levels of each marker and LDL-c. Therefore, the LDL-c values decreased with the increase in the changes of absolute values of each marker induced by ezetimibe administration ; these results reflect the pharmacokinetics of ezetimibe.

Ezetimibe responders

We attempted to determine certain characteristics of the ezetimibe responders. We considered a patient to be an ezetimibe responder if 1) the LDL-c level in that patient reduced by >20% as compared to the initial value and/or 2) the LDL-c level in that patient reduced to <120 mg/dL by eztimibe administration. Among all patients, the first condition was noted in 21 patients and the second in 25 patients ; both conditions were noted in 18 patients. However, no correlation was noted by multivariate regression analysis between ezetimibe efficacy and patient characteristics such as gender, age, and BMI. In addition, neither a diabetic condition nor the administration method of ezetimibe as a monotherapy or in combination with other drugs were found to be related to ezetimibe efficacy, and the initial absolute values of cholestanol, sitosterol, campesterol, and lathosterol were also not related to ezetimibe efficacy.

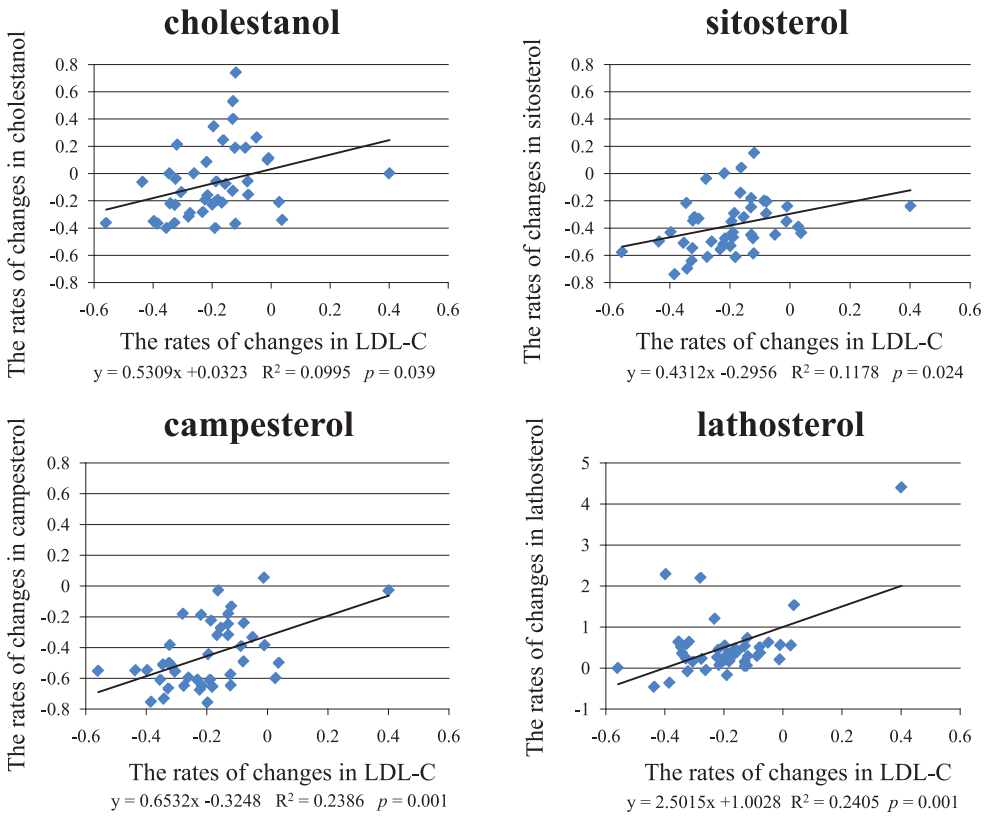

Fig. 1 The scattergram
Correlation between the rates of changes in LDL-c and the rates of changes in each of the cholesterol absorption/synthesis markers.

DISCUSSION

Our study results were compatible with those of a short-term randomized controlled trial (RCT) (21) and other reports (17, 22-25) which showed that ezetimibe was clinically effective in reducing LDL-c when administered as monotherapy or in combination with a statin. The results of our study using absorption/synthesis markers confirmed that ezetimibe selectively inhibits the absorption of cholesterol and is associated with a rebound increase in cholesterol synthesis (26, 27). Previous study reports indicate that ezetimibe administration elevates HDL-c levels and reduces triglyceride levels (4) ; however, these changes were not observed in our study.

Statins have a potent cholesterol-lowering effect, but certain types of statins should be used cautiously because they can impair glycemic control (28, 29). Atorvastatin has been reported in some cases to disrupt glycemic control in patients with type 2 diabetes (30. 31). The mechanism by which atorvastatin disrupt glycemic control remains unknown ; however, atorvastatin was shown to inhibit adipocyte maturation and glucose transporter 4 (Glut4) expression by blocking isoprenoid biosynthesis, thus impairing glucose tolerance (32). In addition, atorvastatin was reported to impair insulin secretion (33) ; this suppressive effect occurs probably because atorvastatin and similar lipophilic statins cause β-cell cytotoxicity and sterol regulatory-element binding protein (SREBP) activation (30). Hiramitsu *et al*. (34) reported that ezetimibe treatment reduces the fasting serum insulin level and HbA1c in the Japanese population. In our study, no statistically significant changes were noted in the levels of the parameters for glucose metabolism in both diabetic and nondiabetic patients when ezetimibe was administered as monotherapy or in combination with a statin. Because the number of patients in this study was small, studies with a larger patient group need to be performed to confirm this result.

From a medical and a socio-economical perspective, it is important to identify "responders" for a certain drug among a patient population. Theoretically, ezetimebe should work more effectively in patients who exhibit high levels of absorption marker, such as cholestanol, sitosterol, and campesterol, or low levels of cholesterol synthesis markers, such as lathosterol ; this hypothesis is based on the pharmacokinetics and effects of ezetimibe and the fact that not all patients respond to statins ; this lack of response is assumed to be because of high rate of absorption and low rate of synthesis of cholesterol observed in some patients (35). Increased cholesterol synthesis has been observed in obese subjects (36), patients with metabolic syndrome (3, 37, 38) and type 2 diabetes patients (39, 40) ; however, an earlier study suggests that cholesterol absorption is increased in obese subjects (41). It was quite interesting to investigate whether patients exhibiting high levels of absorption markers benefited from ezetimibe administration and whether the existence of obesity or diabetes affected ezetimibe efficacy. Diabetic patients have been reported to have higher NPC1L1 mRNA levels than control subjects (42), and thus, we expected that ezetimibe will be more beneficial for diabetic patients. However, the absolute values of cholesterol absorption and synthesis marker were not found to be related with the existence of diabetes or obesity in the likely ezetimibe responders. For a definite answer to this issue, an investigation needs to be conducted on a larger number of patients.

Elevated CRP levels indicate a low-grade inflammation, which is associated with endothelial dysfunction. Previous studies indicate that at all doses, statins when coadministered with ezetimibe induce significantly lower high-sensitivity CRP levels than when administered as monotherapy (43-45) ; this suggests an additional antiinflammatory/anti-atherosclerotic action of the combination therapy. In our study, there were no significant changes noted in the CRP levels in all patients ; however, a significant reduction in the serum levels of high-sensitivity CRP has been reported in the Japanese population (34), the clinical implications of which remain to be studied.

Our study had the following limitations. Ezetimibe was administered for a short period, and the number of the patients studied was small. We also excluded a patient who dropped out during the treatment. Although we had instructed the patients to continue with their normal activities during the study period and conducted the study throughout the year to eliminate seasonal influences, there may be some variations in factors such as diet and exercise, thus affecting lipid profile and glucose metabolism. Finally, the population of only a single ethnicity, i.e., the Japanese, was studied ; the results of a similar study in other ethnic populations may vary.

CONCLUSION

In conclusion, ezetimibe can be considered to be an efficacious and well-tolerated drug for dyslipidemia

on the basis of our study results. Because we were unable to identify the specific characteristics of ezetimibe responders among our subjects, we propose that ezetimibe can be used in any population to lower the LDL-c levels.

REFERENCES

1. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ : Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. J Am Coll Cardiol 44 : 720-732, 2004
2. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y : American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2007 update : a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 115 : e69-e171, 2007
3. Strandberg TE, Tilvis RS, Pitkala KH, Miettinen TA : Cholesterol and glucose metabolism and recurrent cardiovascular events among the elderly. A prospective Study. J Am Coll Cardiol 48 : 708-714, 2006
4. Miettinen TA, Gylling H, Strandberg T, Sarna D : Baseline serum cholesterol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. BMJ 316 : 1127-1130, 1988
5. Heart Protection Study Collaborative Group : MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals : a randomised placebo-controlled trial. Lancet 360 : 7-22, 2002
6. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM : Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 35 : 1495-1504, 2004
7. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK ; Treating to New Targets (TNT) Investigators : Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352 : 1425-1435, 2005
8. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J : Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction : the IDEAL study : a randomized controlled trial. JAMA 294 : 2437-2445, 2005
9. Armitage J : The safety of statins in clinical practice. Lancet 370 : 1781-1790, 2007
10. Harris M., Davis W., Brown WV : Ezetimibe. Drugs of Today 39 : 229-247, 2003
11. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB : Ezetimibe : a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 44 : 467-94, 2005
12. Davies JP, Levy B, Ioannou YA : Evidence for a Niemann-pick C (NPC) gene family : identification and characterization of NPC1L1. Genomics 65 : 137-145, 2000
13. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP : Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science 303 : 1201-1204, 2004
14. Davis HR Jr, Hoos LM, Tetzloff G, Maguire M, Zhu LJ, Graziano MP, Altmann SW : Deficiency of Niemann-Pick C1 Like 1 prevents atherosclerosis in ApoE-/- mice. Arterioscler Thromb Vasc Biol 27 : 841-849, 2007
15. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP : Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. Science 303 : 1201-1204, 2004
16. Derosa G, D'Angelo A, Franzetti IG, Ragonesi PD, Gadaleta G, Scalise F, Ciccarelli L, Piccinni MN, Cicero AF : Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic

hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment. J Clin Pharm Ther 34 : 267-276, 2009
17. Daskalopoulou SS, Mikhailidis DP : Reaching goal in hypercholesterolaemia : dual inhibition of cholesterol synthesis and absorption with simvastatin plus ezetimibe. Curr Med Res Opin 22 : 511-528, 2006
18. Japan Atherosclerosis Society : Japan Atherosclerosis Society (JAS) guideline for prevention of atherosclerotic cardiovascular diseases. J Atheroscler Thromb 5-57, 2007
19. The Committee of Japan diabetes society on the diagnosis criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 1 : 212-228, 2010
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC : Homeostasis model assessment : insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28 : 412-419, 1985
21. Ezetimibe for the treatment of hypercholesterolaemia : a systematic review and economic evaluation. Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, Paisley S, Chilcott J : Ezetimibe for the treatment of hypercholesterolaemia : a systematic review and economic evaluation. Health Technol Assess 12 : 1-212, 2008
22. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP : Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia : a prospective, randomized, double-blind trial. Circulation 107 : 2409-2415, 2003
23. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, Suresh R, Sun S, Veltri EP : Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 40 : 2125-2134, 2002
24. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB, for the Ezetibibe Study Group : Efficacy and safety of ezetimibe coadministered with smvastatin in patients with primary hypercholesterolemia : a randomized,double-blind, placebo-controlled trial. Mayo Clin Proc 79 : 620-629, 2004
25. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J : A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients : The Ezetimibe Add-On to Statin for Effecticeness (EASE) trial. Mayo Clin Proc 80 : 587-595, 2005
26. Hoenig MR, Rolfe BE, Campbell JH : Cholestanol : A serum marker to guide LDL cholesterol-lowering therapy. Atherosclerosis 184 : 247-254, 2006
27. Sudhop T, Lütjohann D, Kodal A, Igel M, Tribble DL, Shah S, Perevozskaya I, von Bergmann K : Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 106 : 1943-1948, 2002
28. Sasaki J, Iwashita M, Kono S : Statins : Beneficial or adverse for glucose metabolism. J Atheroscler Thromb 13 : 123-129, 2006
29. Her AY, Kim JY, Kang SM, Choi D, Jang Y, Chung N, Manabe I, Lee SH : Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther 15 : 167-174, 2010
30. Yamakawa T, Takano T, Tanaka S, Kadonosono K, Terauchi Y : Influence of putavastatin on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb 15 : 269-275, 2008
31. Takano T, Yamakawa T, Takahashi M, Kimura M, Okamura A. Influences of statins on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb 13 : 95-100, 2006
32. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T : Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4) : implications in glycaemic control. Diabetologia 49 : 1881-1892, 2006
33. Ishikawa M, Okajima F, Inoue N, Motomura K, Kato T, Takahahsi A, Oikawa S, Yamada N, Shimano H : Distinct effects of pravastatin, atrovastatin, and simvastatin on insulin secretion from a beta-cell line, MIN6 cells. J Atheroscler Thromb 13 : 329-335, 2006
34. Hiramitsu S, Ishiguro Y, Matsuyama H, Yamada K, Kato K, Noba M, Uemura A, Yoshida S, Matsubara Y, Kani A, Hasegawa K, Hishida H, Ozaki Y : The effects of Ezetimibe on surrogate markers of cholesterol absorption and synthesis in Japanese patients with dyslipidemia. J Atheroscler Thromb 17 : 106-114, 2010

35. Tomkin GH : Ezetimibe-new anti-atherogenic properties? Br J Pharmacol 156 : 1216-1217, 2009
36. Miettinen TA, Gylling H : Cholesterol absorption efficiency and sterol metabolism in obesity. Atherosclerosis 153 : 241-248, 2000
37. Miettinen TA, Gylling H, Viikari J, Lehtimäki T, Raitakari OT : Synthesis and absorption of cholesterol in Finnish boys by serum noncholesterol sterols. The cardiovascular risk in young Finns study. Atherosclerosis 200 : 177-183, 2008
38. Chan DC, Watts GF, Barrett PH, O'Neill FH, Thompson GR : Plasma markers of cholesterol homeostasis and apolipoprotein B-100 kinetics in the metabolic syndrome. Obes Res 11 : 591-596, 2003
39. Pihlajamäki J, Gylling H, Miettinen TA, Laakso M : Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. J Lipid Res 45 : 507-512, 2004
40. Simonen PP, Gylling HK, Miettinen TA : Diabetes contributes to cholesterol metabolism regardless of obesity. Diabetes Care 25 : 1511-1515, 2002
41. Mok HY, von Bergmann K, Grundy SM : Effects of continuous and intermittent feeding on biliary lipid outputs in man : application for measurements of intestinal absorption of cholesterol and bile acids. J Lipid Res 20 : 389-398, 1979
42. Lally S, Tan CY, Owens D, Tomkin GH : Messenger RNA levels of genes involved in dysregulation of postprandial lipoproteins in type 2 diabetes : the role of Niemann-Pick C1-like 1, ATP-binding cassette, transporters G5 and G8, and of microsomal triglyceride transfer protein. Diabetologia 49 : 1008-1016, 2006
43. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E ; ENHANCE Investigators : Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia. N Engl J Med 358 : 1431-43, 2008
44. Pearson TA, Ballantyne CM, Veltri E, Shah A, Bird S, Lin J, Rosenberg E, Tershakovec AM : Pooled analyses of effects on C-reactive protein and low density lipoprotein cholesterol in placebo-controlled trials of ezetimibe monotherapy or ezetimibe added to baseline statin therapy. Am J Cardiol 103 : 369-374, 2009
45. Sager PT, Capece R, Lipka L, Strony J, Yang B, Suresh R, Mitchel Y, Veltri E : Effects of ezetimibe coadministered with simvastatin on C-reactive protein in a large cohort of hypercholesterolemic patients. Atherosclerosis 179 : 361-367, 2005